DETAILED ACTION

1. Currently, claims 1-66 are pending in the instant application. Claims 1-6, 11-14, 18, 21-66 are withdrawn. Claims 7 and 20 has been amended. This action is written in response to applicant's correspondence submitted 02/15/2008. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented, as necessitated by amendment, or are reiterated from the previous office action. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is Final**

2. It is noted that claims 8-10, 15-17 does not comply with 37 CFR 1.121, as it does not have the correct status identifier. In response to this office action, applicant is required to change the status identify of claim 8-10, 15-17 from "withdrawn" to "original". It is noted that in the remarks filed on 02/15/2008 on page 16, applicant indicates that claims 7-10, 15-17 and 20 are under examination. Thus claims 8-10 and 15-17 have been examined, if applicant intends to withdraw these claims and not continue prosecution with respect to these claims applicant should clearly indicate that in the next correspondence.

3. Claims 7-10, 15-17, and 20 are under examination with respect to nucleic acids. Claims 7-10 and 15-17 are under examination with respect to SEQ ID no. 471.

4. The information disclosure statement filed on 06/29/04, 07/29/05, and 02/15/08 have been considered. The initialed SB-08 form for an unrelated application, 11/120435 that was erroneously placed in the application on 08/15/2007 has been removed.

Election/Restrictions

5. Applicant's election with traverse of group 311, SEQ ID No. 471, claims 16-17 in the reply filed on 06/01/2007 is acknowledged. The traversal submitted on 02/26/2007 is on the ground(s) that that the MPEP section 803.04 instructs examiners to search up to 10 nucleotide sequences per application and groups CCCX1-CCCXX recite only ten nucleotides sequences and therefore these groups should be searched and examined. The response further asserts that six of these sequences are duplicates and pose no additional search burden on the examiner. This is not found persuasive because the office rescinded the 1996 waiver of permitting up to ten independent and distinct polynucleotides published in the O.G. notice on March 27, 2007 based upon the increasing computational, search, and examination burden required for the consideration of nucleic acid sequences and complexity of claims drawn to such, compared to the time of the 1996 waiver. Furthermore, applicant did not elect any of the six sequences that are duplicate and therefore the sequence that is examined is SEQ ID No. 471.

The requirement is still deemed proper and is therefore made FINAL.

6. Claims 1-6, 11-14, 18-19, 21-66 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 02/26/2007 and 06/01/2007.

Drawings

7. The drawings are acceptable.

Withdrawn Rejections

8. The rejections of claims 7-9 and 15 under 35 102(b) made in section 8 of the office action mailed 08/15/2007 is withdrawn in view of the amendment to the claims.

9. The rejection of claims 7-9 and 15 under 35 102(b) made in section 9 of the office action mailed 08/15/2007 is withdrawn in view of the amendment to the claims.

Maintained Rejections

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 7-10, 15-17 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was previously presented in section 6 and has been rewritten to address the amendment to the claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The nature of the claims is drawn to evaluating the level of neuropathic pain in a mammal by analyzing the amount of a nucleic acid in skin biopsy sample under conditions of neuropathic pain compared to a second skin biopsy sample under conditions of substantially no neuropathic pain. The claims are further drawn to difference in 2-fold amount of nucleic acid in the first sample compared to second samples. The claims are further drawn to samples from the same mammal. The claims are further drawn to rodent and human. The claims are further limited to the nucleic comprises a nonredunant sequence of SEQ ID No. 471 and the surrogate maker is muscle-specific.

The rejected claims encompass analysis of any mammal, including human and non-human mammals. The rejected claimed encompass analysis of any muscle specific nucleic acid or nonredudant subsequence of SEQ ID no. 471, any difference in the amount of nucleic acid, increase or decrease, and any level of neuropathic pain.

The nature of the claims requires knowledge of a correlation between any muscle specific nucleic acid expression and detection of any level of neuropathic pain in any mammal.

Guidance in the Specification and Working Examples

The specification asserts a method for determining neuropathic pain from obtaining a skin biopsy sample and determining the gene expression levels measured in the skin punch biopsy samples (see paragraph 5 and paragraph 6).

The specification asserts that a difference between the amount of nucleic acid in the first sample and the amount of nucleic acid in the second sample indicates that the nucleic acid is a surrogate marker of neuropathic pain. However the claims are broadly drawn to any amount of nucleic acid, increase or decrease as well as any level of neuorapathic pain and the specification does not teach predictably correlating any expression level with any level of neuropathic pain.

The specification asserts that SEQID No. 471, is in group III, category SMP, and is associated with NM_006063.1 (see table 4). However, the specification does not give any data, expression level, any skin biopsy results of SEQ ID No. 471 or any nonredunant subsequence of SEQ ID No. 471. Furthermore, SEQ ID No. 471 is a human DNA sequence and the specification does not teach any studies, obtaining skin biopsies or working examples of a gene expression analysis of neuropathic pain in humans.

The specification demonstrates a working example of obtaining skin samples from rats post-spinal nerve ligation and analysis of mRNA from skin biopsies profiled on Affymetrix Rat Genome arrays (See examples). However the specification does not demonstrate that the expression levels are predictably correlative to an increase or decrease level of neuropathic pain.

The specification does not demonstrate the amount of neuropathic pain that is associated with the gene expression obtained from the skin biopsies. Furthermore, the data presented in the specification does not predictably correlate any neuropathic pain with an increase in expression, as different neuropathic pains result in different gene expression values in rats (see figure 1, 2, for example).

The specification does not teach a control study, a predictive value, nor a connection between the expressed gene and the neuropathic pain level in either humans or rats. The specification does not teach the "any" type of mammal. The specification does not provide any guidance with the status of the neuropathic pain, for example did the rats have any other diseases that would affect the condition of the skin (for example, diabetes) and possibly affect the gene expression level of the marker genes? Based on the teachings in the specification, it is unclear how the expression level of any muscle specific nucleic acid level would determine the level of neuropathic pain in any mammal.

It is unclear how the skilled artisan would be able to determine the level of neuropathic pain because the specification does not teach which genes are correlative with levels of neuropathic pain in a skin biopsy in any mammal, rodent or human. Furthermore, claims are drawn to detecting the expression level of SEQ ID No. 471 (claim 7), which is a human sequence, and determining the level of neuropathic pain in any mammal. Dependent claims require determining the pain level in a rodent, however it is unclear how a human sequence, SEQ ID No. 471 will be expressed in any mammal other than human and specifically in a rodent.

The following is unclear from the teaching in the specification. The specification does not

teach the analysis of "any" level of neuropathic pain, in "any" mammal by obtaining a skin biopsy and determining the level of "any" muscle-specific nucleic acid. The specification provides no teaching of how the level of neuropathic pain is correlative to gene expression. The specification envisions hypothetical situations where "any" neuropathic pain level can be determined by any expression level of a nucleic acid in a mammal. The specification appears to be conceiving of possible scenarios where the expression level could be determined in a skin biopsy and that these levels could indicate neuropathic pain levels, however, it is unclear how one of skill in the art would determine the level of expression necessary to determine the ability to predictably correlate the level of neuropathic pain level based on the expression level of a nucleic acid.

The unpredictability of the art and the state of the prior art

While the state of the art and level of skill in the art with regard to detection of a gene expression in a biological sample is high, the level of unpredictability in associating any particular expression level of a gene with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art teaches that there are many parameters that need to be evaluated prior to using gene expression as a test to determine the level of neuropathic pain in any mammal. Furthermore, the prior art teaches that the parameters that need to be addressed in order to conduct a study on modulating gene expression yield gaps in information that are needed to complete a thorough screening of gene expression effects.

Shalon et al. (US 2001/0051344 A1 Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a

gene between any two individuals may or may not be significant (see page 10, paragraph 0155). Shalon et al. further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (see page 10, paragraph 0156). Sharlon et al. teach that the test average pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically at least 2 fold and up to 100 fold or more, increase or decrease in gene expression level with respect to control levels for the same gene (see page 10, paragraph 0158). Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph). Additional post filing art

reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 2004, Vol 18, page 20) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (see page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (see page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (see page 3, 2nd paragraph).

Additionally, the prior art teaches the unpredictability of determining neuropathic pain within different species of rats, which further demonstrates the unpredictability of extrapolating the data from rats to human. Lovell et al. (Pharm. Biochem. and Behavoir, 2000, vol. 65:141-144) teach strain-related differences in thermal hyperalgesic response to peripheral nerve injury in rats (see pg. 143, 2nd column, last paragraph). Lovell et al. teach the mechanisms underlying strain difference in behavioral hypersensitivity to thermal nociceptive stimuli are less than clear (see pg. 144, 1st column, last paragraph). Furthermore, Benoliel et al. (Pain 20002, 97:203-212) demonstrate that different strains of rats have different pain tolerances. Benoliel et al. demonstrate that the effect of strains on the extent of measurable behavior parameters have been greatly studied and demonstrate that Lewis rats developed hyerpalgesic responses slower than Sprague-Dawly rats (see pg. 210, last column, last para. con't to next page). Benoliel et al. demonstrate that Sprague Dawly rates and Lewis rats, will vary in response to pain. Therefore, the prior art teaches the unpredictability of neuropathic pain levels among the same species and

demonstrates the unpredictability of extrapolating neuropathic pain levels among different mammal species.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to correletation of any level of expression of a nucleic acid in skin biopsy with the level of neuropathic pain in any mammal, the quantity of experimentation in this area is extremely large. The skilled artisan would have to determine a predictable correlation between any nucleic acid molecule, including the nonredundant subsequence of SEQ ID no. 471, that would be capable of detecting and determining the level of neuropathic pain in all mammal species. To practice the invention as broadly as it is claimed, the skilled artisan would have to determine a gene expression profile in many different mammals with many different types of neuropathic pain and pain levels and then determine if each genes expression profile is changed upon the level and type of neuropathic pain. The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if the gene is in fact detecting neuropathic pain. There is still a significant amount of unpredictably in identifying genes and within the human gene, a skilled artisan would be unable to know if the detected sequence was detecting neuropathic pain and the skilled artisan after detection of the sequence would have to perform a large exhaustive assay to test for gene detection in large study pool to determine the specific genes that identify only neuropathic pain and pain levels . This would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any

guarantee of success in the succeeding steps. Thus given the broad claims in an art whose nature is identified as unpredictable, the lack of guidance on how to predictably correlate gene expression with neuropathic pain levels in any mammal, the large quantity of research required to define the lack of guidance provided in the specification, the absence of working examples, and the negative teaching in the prior art balanced only against the high level of skill in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to make the claimed invention.

Response to Arguments

11. The response traverses the rejection on pages 17-25 of the response mailed 02/15/2008. The response asserts that the amended claims are enabled. The response asserts that the claims do not encompass any nucleic acid but related to either a nonredundant subsequence or are muscle specific. It is noted that the amended claims are drawn to nonredundant subsequence of SEQ ID No. 471 or muscle specific nucleic acids, however this recitation encompasses a large genus of nucleic acids that are not taught in the specification in sufficient detail to enable one of skill in the to make and use the invention with respect to predictably associating the expression level of the large genus of nucleic acid with neuropathic pain in any mammal, including rodent and human.

The response asserts on page 18, that the breadth of the expression level as taught in the working examples demonstrates both increased and decreased expression of different markers. The response further asserts that the claims explicitly cover only methods that work, methods in which the difference detected between the two samples indicates the level of neuropathic pain.

This response has been thoroughly reviewed but not found persuasive. The specification does not teach one of skill in the art which methods explicitly work, the specification lacks the guidance for the skilled artisan to determine which muscle specific nucleic acid expression levels or subsequence of SEQ ID No. 471 would be predictably associated with neuropathic pain, for example the specification does not teach any expression analysis of nucleic acid expression in muscle specific genes in human, dog, cat, horse, etc. and its association with neuropathic pain level and thus the specification is not enabled for the claimed method.

The response asserts on page 19, that the specification provides extensive guidance to the skilled artisan including working examples to the full scope of sequences recited in claim 7. The response asserts that table 2 lists 308 rate sequences that have been shown to be differentially expression under conditions of neuropathic pain in rats and that SEQ ID No. 471-630 are the corresponding human nucleic sequences. This response has been thoroughly reviewed but not found persuasive. The claims is limited to expression analysis of SEQ ID. No. 471, the working example does not show expression analysis of SEQ ID No. 471, thus the working example does not describe the full scope of the sequences recited in claim 7. As demonstrated by Lovell and Benoliel analysis of one species with respect to neuropathic pain can not be extrapolated to the analysis and pain level in other species, even with different species of rats. Thus, it would be entirely unpredictable to correlate the expression level of SEQ ID No. 471, a human nucleic acid sequence with neuropathic pain levels in rats or vice versa, correlate the expression level of a rat sequence to determine the level of neuropathic pain in a human. The specification does not provide any work examples of neuropathic pain level and gene expression analysis of SEQ ID no. 471 or muscle specific genes in human, dog, cat, horse, to which the

claims are broadly drawn. Furthermore, the claims are drawn to detecting the expression level of SEQ ID No. 471, which is a human sequence however dependent claims require determining the pain level in a rodent, it is unclear how a human sequence, SEQ ID No. 471 will be expressed in any mammal other than human and specifically in a rodent.

The response asserts that the specification provides extensive guidance regarding obtaining skin biopsies, animal models, determining and comparing expression levels and method for confirming expression. The response further asserts on page 20 that skilled artisan could practice the full scope of the claims with minimal experimentation and embodiments could be practiced after trivially confirming the expectation that corresponding rat sequences, human sequence are differentially expressed under conditions of neuropathic pain. This response has been thoroughly reviewed but not found persuasive. The examiner agrees that it is routine experimentation to obtain skin biopsy and determining and compare expression level in a sample however it is not routine experimentation to associate the level of neuropathic pain with expression level of nucleic acids in mammals nor it is a trivial to determine expression levels under conditions of neuropathic pain. As demonstrated by Lovell and Benoliel analysis of one species with respect to neuropathic pain can not be extrapolated to the analysis and pain level in other species, even with different species of rats, this it is not trivial to determine neuropathic pain with different species of the same mammal much less extrapolate data to other mammals. It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its*

successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case the association of neuropathic pain with expression level of muscle specific nucleic acids or nonredudant subsequence of SEQ ID No. 471 is not considered routine in the art and without sufficient guidance to a specific process of expression analysis of muscle specific genes and predictably correlation between expression levels and neuropathic pain level in mammals, which includes human, mouse, cat, horse, etc. to achieve a diagnostic outcome the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The response asserts on page 21-22 that the references cited by the Examiner have little or no bearing on the enablement of the claimed invention. The response asserts that Kroese and Lucentini are irrelevant because both relate to genetic testing and the claimed invention does not related to genetic testing. The response asserts that the fact that genetic conditions may be caused by more than one gene have no application in expression based approaches. This response has been thoroughly reviewed but not found persuasive. Lucentini teaches that gene association

studies linking gene to disease is typically wrong. Gene association studies encompass detection of gene expression levels to determine a disease. For example Lucentini teaches that when a study first finds that a gene is associated with a complex disease there is only a one third chance that study will be reliable. Thus, the finding that expression level of one muscle specific nucleic acid with neuropathic pain will not necessarily predictably determine other muscle specific nucleic acids are associated with pain and further research of the first nucleic acid will likely reveal there is no association. Thus, Lucentini demonstrates that linking genes to disease is unpredictably and thus linking gene expression level of muscle specific genes or SEQ ID No. 471 to neuropathic pain is unpredictable.

The response asserts that Shalon merely stands for proposition that expression markers should be identified on basis of statistically significant differences in expression levels. Applicants assert the specification on pages 64-67 performed standard statistical analysis and therefore satisfies the tests for statistical significance. This response has been thoroughly reviewed but not found persuasive as the specification does not teach statistically significant expression levels for the claimed invention. For example the specification does not teach statistical analysis of SEQ ID No. 471 and its association to neuropathic pain in any mammal, including human nor does the specification teach that the expression level of SEQ ID no. 471 is greater than two fold.

The response asserts that Lovelle and Benoliel are irrelevant. The response asserts that Lovelle teaches outbred strains demonstrate significant hperalgesic responses to peripheral nerve injury and these results do not show unpredictability of determining neuropathic pain. The response asserts that inbred strains showed no neuropathic pain and assert that the skilled artisan

would expect the claimed method to yield the same accurate determination. This response has been thoroughly reviewed but not found persuasive. Lovelle teaches that different strains, inbred and outbred strains showed different pain responses thus the pain level within one mammal will be different and therefore the predictability of associating pain levels even within one type of mammal is unpredictable and thus it will be unpredictable to extrapolate pain level from one mammal to pain levels in another mammal as Lovelle teaches that inbred versus outbred strains will have different pain levels.

The response asserts that Benoilele simply teaches that some rat strains expression neuropathy under condition that cause no neuropathy in other strains and that there is no unpredictability of determining neuropathic pain. Benoilele was cited to demonstrate that neuropathic pain can not be extrapolated between different mammals, as even with the same mammal the pain level detected will vary, thus demonstrating the unpredictability of pain levels within even the same mammal. Benoilele shows that different strains have different pain levels and thus based on these teaching and evidence that different stains can have significantly different pain levels, the skilled artisan would conclude that it would be entirely unpredictably to extrapolate the pain level of one mammal to the pain level in a different mammal.

The response asserts that Examiner's concern over the unpredictability of practicing the claimed method in mammal other than rodents and humans does not apply to claim 10 and claim 15. It is noted that claim 7, from which claim 10 depends is drawn to detecting SEQ ID no. 471, which is a human sequence and claim 10 is drawn to detecting a rodent. Thus it unpredictable to practice the claimed method in mammals and is relevant even to claim 10, which is drawn to

rodents, as the specification does not teach that the expression of SEQ ID no. 471 is found in other mammals, specifically rodents as cited in claim 10.

The response asserts on page 23 that the test of enablement is not where experimentation would be required but whether such experimentation would be undue. The response asserts that the skilled artisan starts with the disclosed sequences and need only perform routine experimentation to confirm which sequence are effective surrogate markers for neuropathic pain. The response asserts on page 24 that the specification provides extensive guidance and that the skilled artisan could practice hundreds of embodiments of rats with no experimentation at all and efficacy could be confirmed with a single array based experimentation. The response asserts that the skilled artisan need not be able to predict which sequences will be effective surrogate markers if they can be identified by routine experimentation. This response has been thoroughly reviewed but not found persuasive. The examiner agrees that assaying a biological sample for a nucleic acid expression level is routine experimentation however predictably associating expression level of a nucleic acid with level of neuropathic pain is not routine experimentation. As show by Lucentini and Shalon, gene expression studies are typically wrong and require changes in expression that are greater than two, which is not necessarily predictable. The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if the gene is in fact detecting neuropathic pain. There is still a significant amount of unpredictably in identifying genes and within the human gene, a skilled artisan would be unable to know if the detected sequence was detecting neuropathic pain and the skilled artisan after detection of the sequence would have to perform a large exhaustive assay to test for gene detection in large study pool to determine the specific genes that identify only neuropathic pain

and pain levels . This would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Additionally, the skilled artisan would have to determine if the human sequence of SEQ ID No. 471 is expressed in other species and then determine if this expression level of a human gene in different mammals is indicative of pain. Thus given the broad claims, in an art whose nature is identified as unpredictable, the lack of guidance on how to predictably correlate gene expression with neuropathic pain levels in any mammal, the large quantity of research required to define the lack of guidance provided in the specification, the absence of working examples, and the negative teaching in the prior art balanced only against the high level of skill in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to make the claimed invention. Additionally, It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 20 is rejected under 35 U.S.C. 102(b) as being anticipated by Terenghi et al. (cited on IDS).

Terenghi et al. teach obtaining skin calf biopsies from six diabetic and six controls Patients (see pg. 34, 1st column, 2nd full paragraph). Terenghi et al. teach an increase in TrkA (muscle specific, claim 20) mRNA expression compared to normal control (see figure 2). Terenghi et al. teach the first and both sets of skin biopsy samples are obtained from humans (see pg. 34, 1st column, 2nd full paragraph) (claims 9 and 15).

14. Claim 20 is rejected under 35 U.S.C. 102(b) as being anticipated by Diemel et al. (Diabetic Medicine, 1999, vol. 16, pp. 113-118, cited on IDS).

Diemel et al. teach measuring mRNA expression level of NGF (claim 20, muscle specific) in skin biopsies of 19 diabetic patients compared with samples from eight controls (see abstract). Diemel et al. teach an increase in 4 to 14 fold mRNA expression in diabetic patients (See figure 1) (claim 8). Diemel et al. teach the first and second samples were obtained from humans (claim 9 and 15) (see pg. 114, 1st column, last paragraph). Diemel et al. teach that the increase in NGF indicates the level of neuropathic pain (see pg. 117, table 1, 1st column, 2nd paragraph, and abstract).

Response to Arguments

15. The response traverses the rejections on page 25-26 of the remarks mailed 02/15/2008. The response asserts that the mRNA taught by Terenghi and Diemel are not muscle specific. The response asserts that the trkA and NFG are expressed by neurons. This response has been thoroughly reviewed but not found persuasive. It is noted that the claim is drawn to a nucleic acid that is expressed in the skin and that the nucleic acid is muscle specific. Thus, as the claim

requires expression of the nucleic acid in both the skin and muscle, the nucleic acid can be just specific to expression only in the muscle and the claim has been interpreted to encompass a nucleic acid that has the property of being expressed, at some level, in both skin and muscle. Thus, the claims merely require a nucleic acid that is muscle specific, i.e. some level of expression is found in the muscle and/or nucleic acid levels that can be measured in the muscle. Diemel et a. teach NFG levels are decreased in the leg muscles of rats (see pg. 114, 1st paragraph), thus demonstrating that NFG is muscle specific. Furthermore, Yamamoto et al. (Nuerochemical Research, 1996, pp. 929-938) teaches that NGF and trkA is weakly expressed in muscle (see figure 4 and pg. 931, 1st column, 1st para). Thus the teaching of Diemel and Terenghi teach expression levels of nucleic acid from skin biopsies where the nucleic acid is muscle specific.

Conclusion

16. No claims are allowable.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAE BAUSCH whose telephone number is (571)272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Sarae Bausch/
Primary Examiner, Art Unit 1634